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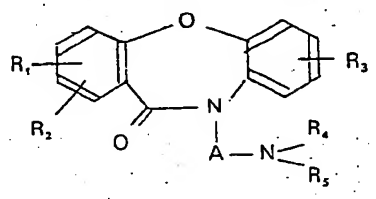
(54) Dibenz(b,f)(1,4)oxazepine derivatives, process for preparing the same, and pharmaceutical composition comprising the same.

(57) Dibenz[b,f][1,4]oxazepine derivatives of the formula



(wherein R_1 is a hydrogen atom or a lower alkyl group; R_2 is a branched lower alkyl group; R_3 is a hydrogen atom, a carboxyl group, a carbamoyl group, a lower alkoxycarbonyl group, or a lower alkoxy group; R_4 and R_5 are each a lower alkyl group or may, when taken together with a nitrogen atom, form a heterocyclic ring; and A is a lower alkylene group) or salts thereof, a process for preparing the same and pharmaceutical compositions comprising the same are disclosed. The derivatives of the formula above are effective in preventing and treating circulatory diseases, especially angina pectoris, and therefore useful as medicines.

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December 21, 1981

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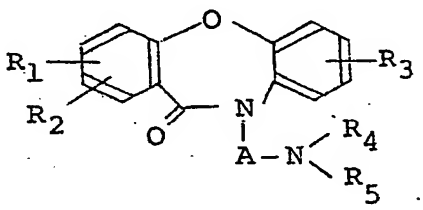
"DIBENZ[b,f][1,4]OXAZEPINE DERIVATIVES, PROCESS FOR PREPARING THE SAME, AND PHARMACEUTICAL COMPOSITIONS COMPRISING THE SAME"

The present invention relates to compounds of the formula:



(I)

(wherein R_1 is a hydrogen atom or a lower alkyl group; R_2 is a branched lower alkyl group; R_3 is a hydrogen atom, a carboxyl group, a carbamoyl group, a lower alkoxycarbonyl group, or a lower alkoxy group; R_4 and R_5 are each a lower alkyl group or may, when taken together with a nitrogen atom, form a heterocyclic ring; and A is a lower alkylene group) or salts thereof.

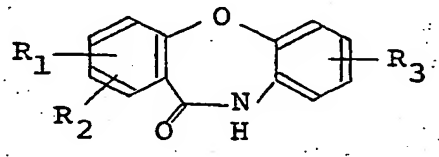
In the formula (I), the lower alkyl group represented by R_1 is a straight or branched alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, isobutyl, n-pentyl, isopentyl, neopentyl and n-hexyl. The branched lower alkyl group represented by R_2 is a branched alkyl group having 3 to 6 carbon atoms, such as isopropyl, sec-butyl, tert-butyl, isobutyl, isopentyl, neopentyl, tert-pentyl and sec-pentyl. The lower alkoxycarbonyl group represented by R_3 is an alkoxycarbonyl group having 2 to 7 carbon atoms, such as methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, n-butoxycarbonyl, n-pentylcarbonyl, and n-hexylcarbonyl. The lower alkoxy

group represented by R_3 is a straight or branched alkoxy group having 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, isobutoxy, n-pentyloxy, sec-pentyloxy, tert-pentyloxy, isopentyloxy, neopentyloxy, and n-hexyloxy. The lower alkyl group represented by R_4 and R_5 is a straight or branched alkyl having 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, and isobutyl. Examples of the heterocyclic ring formed by R_4 and R_5 when they are taken together with a nitrogen atom are piperidino, piperazino, pyrrolidino and morpholino. The lower alkylene group represented by A is a straight or branched alkylene group having 2 to 6 carbon atoms, such as ethylene, trimethylene, tetramethylene, pentamethylene and hexamethylene.

The compounds of the present invention that are represented by the formula (I) are novel compounds effective in preventing and treating circulatory diseases, especially angina pectoris.

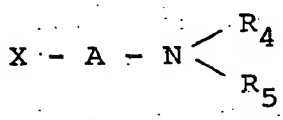
Conventionally known dibenz[b,f][1,4]oxazepine-11(10H)-one derivatives, particularly those having an alkylaminoalkyl group bonded to 10-position, are 10-[2-(dimethylamino)ethyl or 3-(dimethylamino)propyl]-2-methyl-dibenz[b,f][1,4]-oxazepine-11(10H)-one [R_1=H, R_2=CH_3, R_3=H, R_4=R_5=CH_3, A=$(CH_2)_2$ or $(CH_2)_3$ in the formula (I)]; see Swiss Patent No. 421,109. These compounds are said to have emotion control and anti-depression activities, but no data have been presented to support these activites. The present inventors have done experiments to prepare a series of dibenz[b,f][1,4]oxazepine derivatives and test their pharmacological efficacies to review the correlation of their structure and activity. As a result, they have found that compounds having a branched lower alkyl group introduced in the benzene nucleus have desired effects on circulatory organs.

The compounds of the present invention having the formula (I) are prepared by reacting, for example, a corpound of the formula (II):



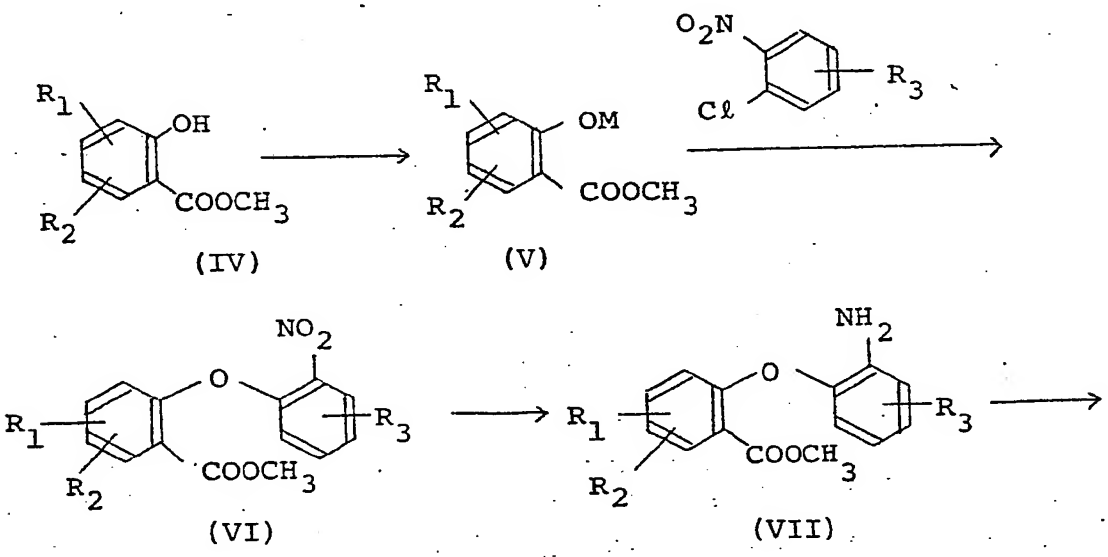
(II)

(wherein R_1, R_2 and R_3 have the same meanings as defined above) with a compound of the formula (III):



(wherein A, R_4 and R_5 have the same meanings as defined above; X is a halogen atom). The reaction is usually performed in the presence of a solvent such as dimethylformamide, dimethyl sulfoxide or dioxane at a temperature between room temperature and 150°C, preferably between 50 and 100°C. Preferably, the compound (II) is preliminarily reacted with an alkali metal into an alkali derivative. Suitable alkali metal sources include sodium amide, sodium hydride, metallic sodium, sodium alcoholate, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, potassium hydroxide, sodium acetate and potassium acetate.

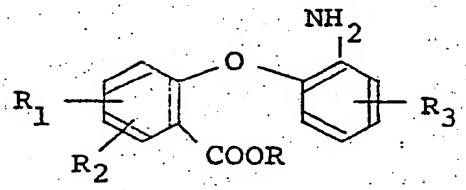
Many of the compounds (II) are also novel compounds which are prepared by taking the following reaction scheme (wherein the same symbols as used in formula (I) have the same meanings; and M is an alkali metal):



To be more specific, a compound of the formula (IV) is converted to an alkali metal salt of the formula (V) which is reacted with an equimolar amount of substituted nitro-

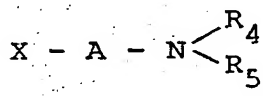
chlorobenzene in the absence of a solvent or in the presence of a solvent such as benzene xylene dimethylformamide or dioxane at a temperature between 80 and 180°C, to thereby obtain a compound of the formula (VI). A good result is obtained if a copper compound is used as a catalyst for the conversion of the compound (V) to the compound (VI). Then, the compound (VI) is catalytically reduced to a compound (VII) in a hydrogen stream at atmospheric or higher pressure in the presence of a catalyst such as palladium-carbon or Raney-nickel. The compound (VII) is subjected to ring formation in the absence of a solvent or in the presence of a solvent at a temperature between 100 and 250°C, preferably between 150 and 200°C, to thereby produce a compound of the formula (II).

The compound of the formula (I) can also be prepared by reacting a compound of the formula (VIII):



(VIII)

(wherein R_1, R_2 and R_3 have the same meanings as defined above; and R is a lower alkyl group) with a compound of the formula (III):



(wherein R_4, R_5, A and X have the same meanings as defined above). The reaction is usually performed in a solvent such as dimethylformamide, dimethyl sulfoxide or dioxane in the presence of an alkali metal at a temperature between room temperature and 150°C, preferably between 50 and 100°C. Suitable alkali metal sources include sodium amide, sodium hydride, metallic sodium, sodium alcoholate, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, potassium hydroxide, sodium acetate, and potassium acetate.

The so prepared compounds of the present invention are useful as a medicine to prevent and treat circulatory diseases.

especially angina pectoris. The compounds can be used as a medicine in the form of tablets, granules, powders, capsules or injections which are made by known method after being blended with a pharmaceutically acceptable carrier and optionally an adjuvant. Preferred pharmaceutical carriers for making tablets, granules, powders and capsules are lactose, starch, dextrin, mannitol, sucrose, crystalline cellulose, kaolin, calcium carbonate, talc, and magnesium stearate. For making an injection, the compounds are preferably dissolved in distilled water or an aqueous solution of salts such as sodium chloride and potassium chloride. The compounds are contained in these formulations in a convenient unit dose that varies with the age of the patient and the severity of his complaints. The daily dose of the compounds is preferably between 100 and 1000 mg for oral administration, and between 10 and 200 mg for intravenous injection.

The present invention is now described in greater detail by reference to the following experiment and examples to which the present invention is by no means limited.

Experiment

The effect of the compounds of the present invention in inhibiting coronary vasoconstriction was studied. This vasoconstriction was induced by acetylcholine 0.3 µg in isolated, donor-perfused rat hearts (K. Sakai, Brit. J. Pharmacol., 68, 625-638, 1980), and determined by measuring the arterial perfusion pressure with a pressure transducer (Nihon Kohden MPU-0.5). The compounds of the present invention were administered in the artery in an amount between 30 and 60 µg. The results are shown in Table 1.

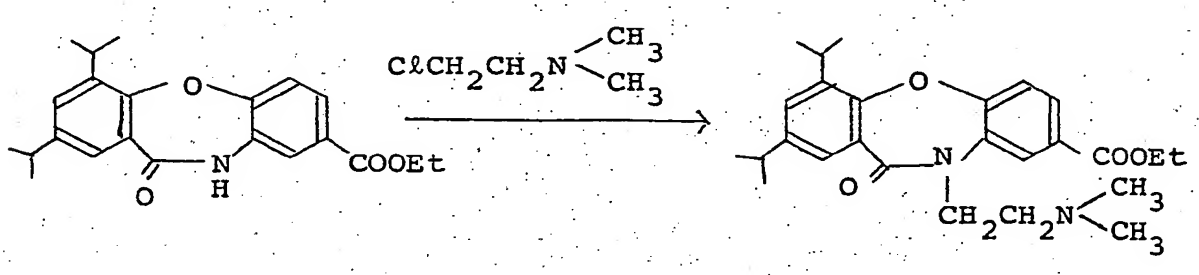
Table 1

Sample	Dose (µg)	Inhibition*
Comp. of Ex. 1	30	++++
Comp. of Ex. 2	30	+++
Comp. of Ex. 3	30	++++
Comp. of Ex. 4	60	++
Comp. of Ex. 5	30	++
Comp. of Ex. 8	30	+++
Comp. of Ex. 9	30	++++
Comp. of Ex. 10	30	++
Comp. of Ex. 14	30	+++
Comp. of Ex. 15	30	++
Comp. of Ex. 17	30	++
dipyridamole	60	±

* ++: 20-30% inhibited
+++: 31-40% inhibited
++++: 41% or more inhibited

Thirty micrograms of an intraarterial injection of the compounds of the present invention proved very effective in suppressing coronary vasoconstriction without presenting an undesired effect similar to that of atropine. Thus, the compounds can be used as a medicine to prevent and treat variant antina pectoris by virtue of a new mechanism. The toxicity of the compounds was found to be very low since the LD_{50} for oral administration to rats was 1 g/kg or more.

Example 1



Two grams of 60% sodium hydride/mineral oil that had been washed once with dry n-hexane was suspended in 100 ml of dry dimethylformamide. To the suspension, 18.4 g of 2,4-

diisopropyl-8-ethoxycarbonyl-dibenz[b,f][1,4]oxazepine-11(10H)-one was added gradually under a nitrogen stream with stirring, and the mixture was heated at 60°C for 30 minutes. Then, 21.6 g of dimethylaminoethyl chloride hydrochloride converted with 50% potassium hydroxide into a free base was extracted with 50 ml of toluene, the extract was added to the previously prepared mixture, and the resulting reaction mixture was heated at 80°C for 7 hours with stirring. The reaction mixture was concentrated under reduced pressure to give a oily residue, which was extracted with 500 ml of benzene. The extract was washed with 200 ml of water three times, and dried over anhydrous Glauber's salt. Then, benzene was distilled off to give 2,4-diisopropyl-10[2-(dimethylamino) ethyl]-8-ethoxycarbonyl-dibenz[b,f][1,4]oxazepine-11(10H)-one as an oil. The product was dissolved in 30 ml of 10% hydrochloric acid-ethanol, and then 100 ml of ethyl ether were added. The resulting crystal was filtered off, and dried to obtain 16 g of a hydrochloride of the product in a yield of 67.2%. Recrystallization from isopropyl alcohol gave a substance having m.p. 233-234°C (with decomposition).

Elemental analysis:

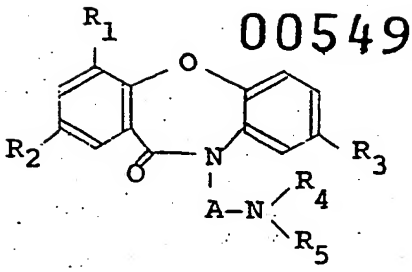
Calculated for $C_{26}H_{34}N_2O_4 \cdot HCl$: C 65.74, H 7.43, N 5.90 (%)

Found : C 65.61, H 7.49, N 5.90 (%)

Examples 2 to 14

The compounds indicated below were prepared as in Example 1.

Table

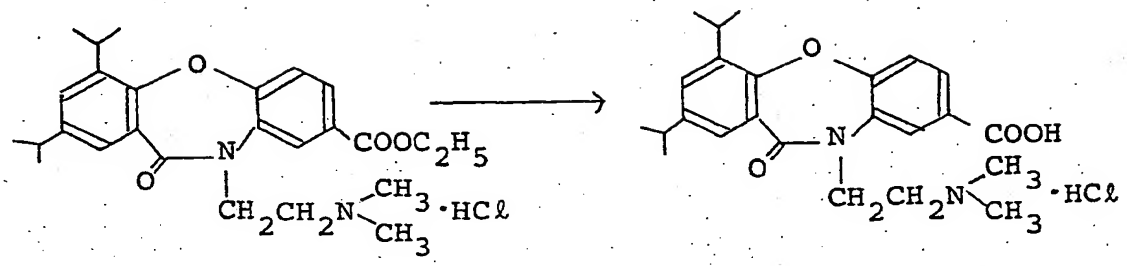


Ex. No.	substituent and its position						m.p. (°C)
	R_1	R_2	R_3	R_4	R_5	A	
2	$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	H	CH_3	CH_3	C_2H_4	204
3	$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	H	CH_3	CH_3	C_3H_6	183
4	$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	OCH_3	CH_3	CH_3	C_2H_4	237
5	$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	OCH_3	CH_3	CH_3	C_3H_6	218
6	$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	$COOC_2H_5$			C_2H_4	216 (with decomposition)
7	$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	$COOC_2H_5$			C_2H_4	222 (with decomposition)
8	H	$t\text{-}C_5H_{11}$	$COOC_2H_5$	CH_3	CH_3	C_2H_4	127
9	H	$t\text{-}C_5H_{11}$	$COOC_2H_5$	CH_3	CH_3	C_3H_6	amorphous powder
10	H	$t\text{-}C_5H_{11}$	H	CH_3	CH_3	C_3H_6	amorphous powder
11	$t\text{-}C_4H_9$	$t\text{-}C_4H_9$	$COOC_2H_5$	CH_3	CH_3	C_2H_4	206
12	H	$t\text{-}C_4H_9$	$COOC_2H_5$	CH_3	CH_3	C_2H_4	127
13	H	$t\text{-}C_4H_9$	$COOC_2H_5$	CH_3	CH_3	C_3H_6	179
14	$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	$COOC_2H_5$	CH_3	CH_3	C_3H_6	124

Table (continued)

Ex. No.	yield (%)	molecular formula	elemental analysis (%)			
				C	H	N
2	72.2	$C_{23}H_{30}O_2N_2 \cdot HCl \cdot \frac{1}{2}H_2O$	calculated	67.72	7.91	6.87
			found	68.01	7.61	6.81
3	72.0	$C_{24}H_{32}O_2N_2 \cdot HCl \cdot \frac{1}{2}H_2O$	calculated	67.68	8.05	6.58
			found	67.46	7.84	6.56
4	64.0	$C_{24}H_{32}O_3N_2 \cdot HCl \cdot \frac{1}{2}H_2O$	calculated	65.22	7.75	6.34
			found	65.46	7.58	6.17
5	44.0	$C_{25}H_{34}O_3N_2 \cdot HCl \cdot \frac{1}{2}H_2O$	calculated	65.85	7.96	6.14
			found	65.62	7.81	6.07
6	85.3	$C_{29}H_{38}O_4N_2 \cdot HCl$	calculated	67.63	7.63	5.44
			found	67.43	7.69	5.48
7	84.3	$C_{28}H_{36}O_4N_2 \cdot HCl$	calculated	67.12	7.44	5.59
			found	67.08	7.46	5.56
8	50.0	$C_{25}H_{32}O_4N_2 \cdot HCl \cdot \frac{3}{2}H_2O$	calculated	61.53	7.44	5.74
			found	61.25	7.18	5.83
9	56.0	$C_{26}H_{34}O_4N_2 \cdot HCl \cdot \frac{3}{2}H_2O$	calculated	62.22	7.63	5.58
			found	62.51	7.56	5.84
10	69.8	$C_{23}H_{30}O_2N_2 \cdot HCl \cdot \frac{3}{2}H_2O$	calculated	64.25	7.97	6.52
			found	64.26	7.72	6.55
11	55.9	$C_{28}H_{38}O_4N_2 \cdot HCl$	calculated	66.85	7.81	5.57
			found	66.63	7.92	5.43
12	59.6	$C_{24}H_{30}O_4N_2 \cdot HCl \cdot H_2O$	calculated	62.00	7.15	6.02
			found	61.76	6.86	5.93
13	50.6	$C_{25}H_{32}O_4N_2 \cdot HCl$	calculated	65.14	7.21	6.07
			found	64.87	7.38	5.85
14	55.6	$C_{27}H_{36}N_2O_4 \cdot HCl$	calculated	66.31	7.62	5.72
			found	66.07	7.34	5.68

Example 15



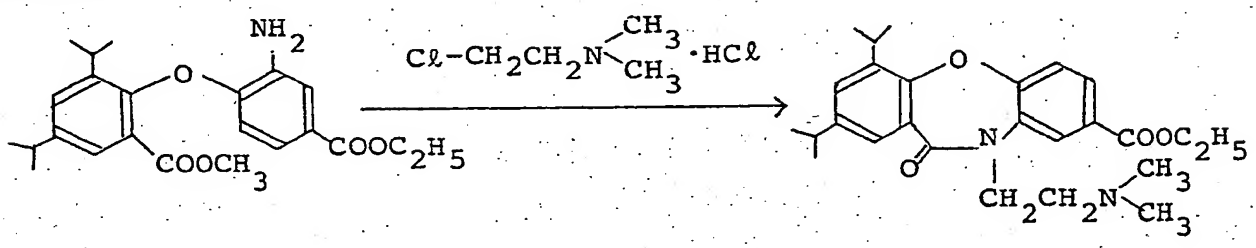
A mixture of 6 g of 2-4-diisopropyl-10-[2-dimethylaminoethyl]-8-ethoxycarbonyl-dibenz[b,f][1,4]oxazepine-11(10H)-one hydrochloride obtained in Example 1, 60 ml of ethanol, and 60 ml of 10% aqueous sodium hydroxide was refluxed for one hour. The mixture was made acidic with diluted hydrochloric acid, and after distilling ethanol off, the mixture was extracted with chloroform containing 5% ethanol. The extract washed with saturated brine and dried over anhydrous Glauber's salt evaporated off to give 5 g of 2,4-diisopropyl-10-[2-(dimethylamino)ethyl]-8-carboxy-dibenz[b,f][1,4]-oxazepine-11(10H)-one hydrochloride in a yield of 88.8% m.p. 245°C (with decomposition) after recrystallization from acetone.

Elemental analysis:

Calculated for $C_{24}H_{30}O_4N_2 \cdot HCl$: C 64.49, H 6.99, N 6.27 (%)

Found : C 64.48, H 6.97, N 6.23 (%)

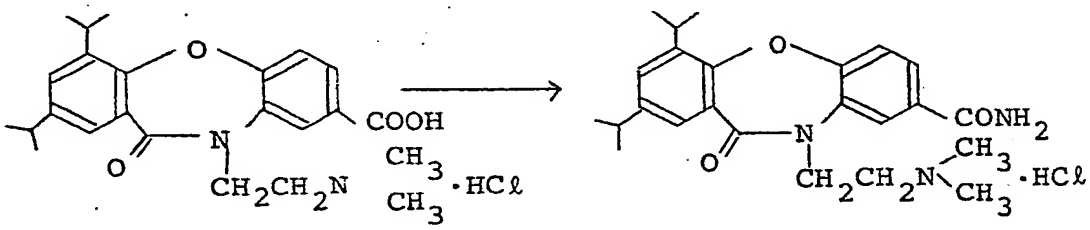
Example 16



Two hundred milligrams of 60% sodium hydride/mineral oil were washed with dry n-hexane once and suspended in 10 ml of dry dimethylformamide. To the suspension, 2 g of methyl 3,5-diisopropyl-2-(4'-ethoxycarbonyl-2'-aminophenoxy)benzoate was added under a nitrogen stream with stirring, and the mixture was heated at 60°C for one hour. Then, 720 mg of dimethylaminoethyl chloride hydrochloride that had been converted with 50% potassium hydroxide into a free base was extracted

with 10 ml of toluene, the extract was added to the previously prepared mixture, and the resulting reaction mixture was heated at 70°C for 7 hours with stirring. The reaction mixture was cooled, mixed with 50 ml of toluene. The toluene layer was washed with 50 ml of water three times, dried over anhydrous Glauber's salt, and then distilled off under vacuum to produce an oily product. The product was purified by column chromatography on silica gel using chloroform-methanol as eluent to give 1.5 g of 2,4-diisopropyl-10-[2-(dimethylamino)ethyl]-8-ethoxycarbonyl-dibenz[b,f][1,4]-oxazepine-11(10H)-one in a yield of 68.2%. Recrystallization from ethanol-water produced a substance having m.p. 97-98°C. The substance was dissolved in 5 ml of 10% hydrochloric acid-ethanol, and the solution was mixed with ethyl ether to produce a hydrochloride of the substance having m.p. 233-234°C (with decomposition). IR analysis of the hydrochloride showed that it was identical with the product of Example 1.

Example 17

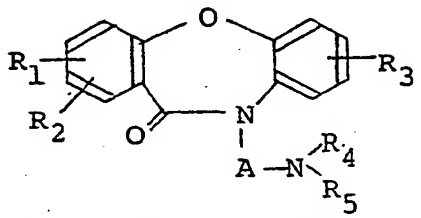


A mixture of 2 g of the 2,4-diisopropyl-10-[2-(dimethylamino)ethyl]-8-carboxy-dibenz[b,f][1,4]oxazepine-11(10H)-one hydrochloride obtained in Example 14, 30 ml of chloroform and 10 ml of thionyl chloride was refluxed for 3 hours. The reaction mixture was concentrated to dryness under vacuum, the residue was mixed with 6 g of ammonium carbonate and 20 ml of chloroform, and the mixture was overnight at room temperature. Then, the reaction mixture was washed with water, dried over anhydrous Glauber's salt, and distilled off to obtain the residue as an oil. The oil was purified by column chromatography on silica gel using chloroform-methanol as eluent to obtain 1 g of 2,4-diisopropyl-10-[2-(dimethylamino)ethyl]-8-carbamoyl-dibenz

[b,f][1,4]oxazepine-11(10H)-one as an oil in a yield of 54.6%. The oil was dissolved in 4 ml of 10% hydrochloric acid-ethanol and left to stand until a hydrochloride of the oxazepine was produced in a crystalline form. m.p. 223-225°C.

We claim:

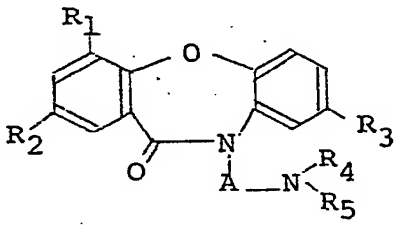
1. A compound of the formula:



(I)

(wherein R_1 is a hydrogen atom or a lower alkyl group; R_2 is a branched lower alkyl group; R_3 is a hydrogen atom, a carboxyl group, a carbamoyl group, a lower alkoxycarbonyl group or a lower alkoxy group; R_4 and R_5 are each a lower alkyl group or may, when taken together with a nitrogen atom, form a heterocyclic ring; A is a lower alkylene group) or a salt thereof.

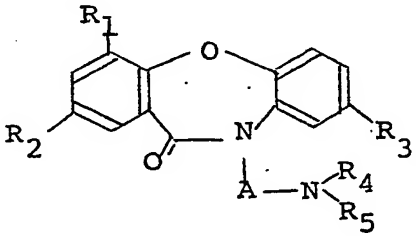
2. A compound according to Claim 1 which is represented by the formula:



(Ia)

(wherein R_1 is a hydrogen atom or a lower alkyl group; R_2 is a branched lower alkyl group; R_3 is a hydrogen atom, a carboxyl group, a carbamonyl group, a lower alkoxycarbonyl group or a lower alkoxy group; R_4 and R_5 are each a lower alkyl group or may, when taken together with a nitrogen atom, form a heterocyclic ring; A is a lower alkylene group) or a salt thereof.

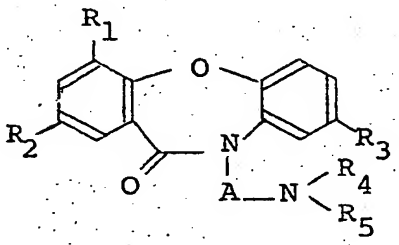
3. A compound according to Claim 1 which is represented by the formula:



(Ia)

(wherein R_1 is a hydrogen or an alkyl group having 1 to 6 carbon atoms; R_2 is a branched alkyl group having 3 to 6 carbon atoms; R_3 is a hydrogen atom, a carboxyl group, a carbamoyl group, an alkoxycarbonyl group having 2 to 7 carbon atoms or an alkoxy group having 1 to 6 carbon atoms; R_4 and R_5 are each an alkyl group having 1 to 4 carbon atoms, or may, when taken together with a nitrogen atom, form a heterocyclic ring; A is an alkylene group having 2 to 6 carbon atoms) or a salt thereof.

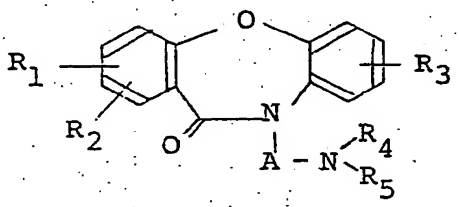
4. A compound according to Claim 1 which is represented by the formula:



(Ia)

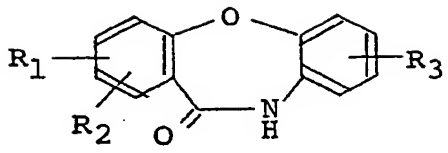
(wherein R_1 is a hydrogen atom, isopropyl or tert-butyl; R_2 is isopropyl, tert-butyl or tert-pentyl; R_3 is a hydrogen atom, methoxy, ethoxycarbonyl, carboxyl or carbamoyl; R_4 and R_5 are methyl or, when taken together with a nitrogen atom, form a piperidyl or pyrrolidinyl; A is ethylene or propylene) or a salt thereof.

5. A process for preparing a compound of the formula:



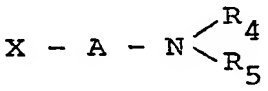
(I)

(wherein R_1 is a hydrogen atom or a lower alkyl group; R_2 is a branched lower alkyl group; R_3 is a hydrogen atom, a carboxyl group, a carbamoyl group, a lower alkoxycarbonyl group or a lower alkoxy group; R_4 and R_5 are each a lower alkyl group or may, when taken together with a nitrogen atom, form a heterocyclic ring; A is a lower alkylene group) or a salt thereof by (1) reacting a compound of the formula:



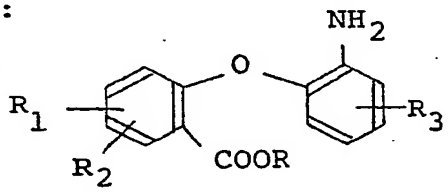
(II)

(wherein R_1, R_2 and R_3 have the same meanings as defined above) with a compound of the formula:



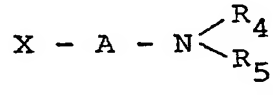
(III)

(wherein A, R_4 and R_5 have the same meanings as defined above; X is a halogen atom), or by (2) reacting a compound of the formula:



(VIII)

(wherein R_1, R_2 and R_3 have the same meanings as defined above; R is a lower alkyl group) with a compound of the formula:



(III)

(wherein A, R_4, R_5 and X have the same meanings as defined above).

6. A process according to Claim 5 wherein the reaction (1) is performed in a solvent such as dimethylformamide, dimethylsulfoxide and dioxane.

7. A process according to Claim 5 wherein the reaction (1) is performed at a temperature between room temperature and 150°C.

8. A process according to Claim 7 wherein the reaction temperature is between 50 and 100°C.

9. A process according to Claim 5 wherein the reaction (1) is performed in the presence of an alkali metal source such as sodium amide, sodium hydride, metallic sodium, sodium alcoholate, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, potassium hydroxide, sodium acetate and potassium acetate.

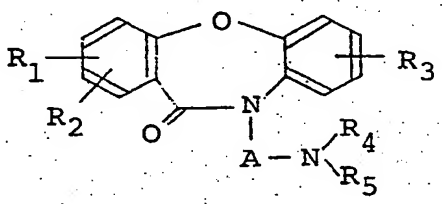
10. A process according to Claim 5 wherein the reaction (2) is performed in a solvent such as diemthylformamide, dimethyl sulfoxide and dioxane.

11. A process according to Claim 5 wherein the reaction (2) is performed at a temperature between room temperature and 150°C.

12. A process according to Claim 11 wherein the reaction temperature is between 50 and 100°C.

13. A process according to Claim 5 wherein the reaction (2) is performed in the presence of an alkali metal source such as sodium amide, sodium hydride, metallic sodium, sodium alcoholate, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, potassium hydroxide, sodium acetate and potassium acetate.

14. A pharmaceutical composition for preventing and treating circulatory diseases which comprises a compound of the formula:



(I)

(wherein R_1 is a hydrogen atom or a lower alkyl group; R_2 is a branched lower alkyl group; R_3 is a hydrogen atom, a carboxyl group, a carbamoyl group, a lower alkoxycarbonyl group or a lower alkoxy group; R_4 and R_5 are each a lower alkyl group or may, when taken together with a nitrogen atom, form a heterocyclic ring; A is a lower alkylene group) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

15. Use of the compounds of the formula I to prepare a pharmaceutical composition for preventing and treating circulatory diseases.

0054951

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number
EP 81 11 0655

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
Y	GB - A - 1 042 296 (D.A. WANDER) * Claims, examples 4-5 *	1-14
Y	FR - A - 0 004 500 (SOC.D'ETUDES SCIENT. ET INDUSTR. DE L'ILE DE FRANCE) * Abstract *	1,5,9, 14
A	DE - A - 1 670 414 (CIBA) * Claims *	1
A	US - A - 3 423 402 (KUPPUSWAMY NAGARAJAN) * Claims *	1-9, 14

CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

C 07 D 267/20
A 61 K 31/645

TECHNICAL FIELDS SEARCHED (Int. Cl.³)

C 07 D 267/00
413/00
A 61 K 31/00

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-14

Claims searched incompletely:

Claims not searched: 15

Reason for the limitation of the search: Method for treatment of the human or animal body by surgery or therapy (see article 52 (4) of the European Patent Convention)

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same category
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons

&: member of the same patent family, corresponding document

Place of search	Date of completion of the search	Examiner
The Hague	15-03-1982	NUYTS

EPO Form 1505.1 06.78